Antipsychotic Drug Impact on Dopaminergic Neurons

Alex D. Klausing (Mentor – Dr. Lane Wallace)
Division of Pharmacology, College of Pharmacy,
The Ohio State University, Columbus, OH

Introduction

The big picture is to explain the effects of antipsychotic drugs on striatal dopaminergic varicosities.

Dopamine neurons are involved in

- –interpreting reward/pleasure
- –converting motivation into action
- –comparing expected and predicted outcomes
- –initiating voluntary movements

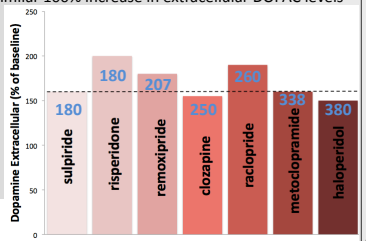
Antipsychotic drugs

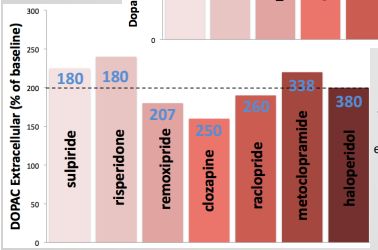
- –control many symptoms of schizophrenia
- –are antagonists at dopamine D2 receptors
- –vary substantially in effects on dopamine varicosities

Literature Data Review

- –All antipsychotics
  - ○No effect tissue dopamine levels
  - ○Similar 80% increase in extracellular dopamine levels
  - ○Similar 100% increase in extracellular DOPAC levels

This figure shows dopamine extracellular levels elicited by antipsychotic drugs. Increase in red shading shows the amount of increase in dopamine synthesis elicited by the drug

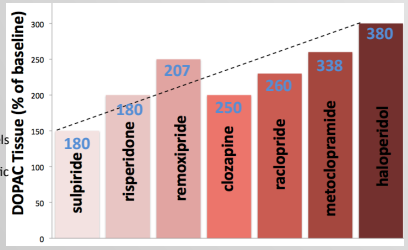




This figure shows DOPAC extracellular levels elicited by antipsychotic drugs

- –Variable effect (80-300% increase) in dopamine synthesis
- –Variable effect (50-200% increase) in tissue DOPAC levels

This figure shows dopamine cytosol levels elicited by antipsychotic drugs

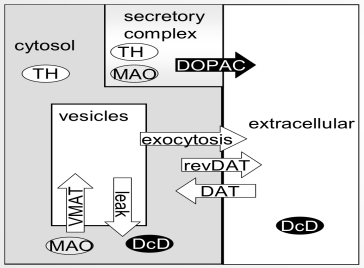


Goal

Goal is to determine a mechanism that explains the effects of antipsychotic drugs on dopaminergic neurons, specifically the variable differences in dopamine synthesis rates and tissue DOPAC levels.

Computational Model

A computation model of a striatal dopaminergic varicosity was used. In the figure below, processes that change species within a compartment, usually enzymes, are shown as ovals. Processes moving molecules across membranes are shown as arrows. Processes affecting only dopamine are shown as white symbols. Processes affecting only DOPAC are shown as black symbols.



Abbreviations are TH, tyrosine hydroxylase; MAO, monoamine oxidase, DAT, dopamine transporter; revDAT, reverse of DAT; VMAT, vesicular monoamine transporter; DcD, processes that remove DOPAC from cytosol; DeD, processes that remove DOPAC from extracellular compartment.

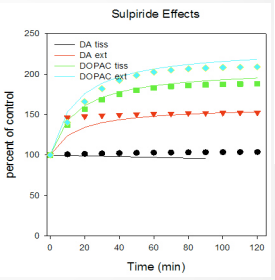
Strategy used to complete the simulations includes

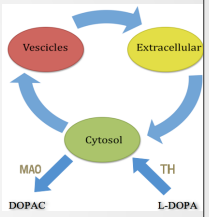
- – Quantitative formulas involving rate constants, affinities, and capacities are assigned to each parameter (arrows and ovals in the diagram).
  - ○ Determined using known biochemical data whenever possible
  - ○ Determined by trial and error if necessary
- – An initial value is assigned for dopamine and DOPAC in all compartments
- – At each program iteration:
  - ○ The amount of dopamine and DOPAC in each compartment is calculated by adding or subtracting to the previous level the amount added or removed from compartments by synthesis/metabolism and how much dopamine and DOPAC was moved between compartments by transport/diffusion
- – Drug effects simulated by changing parameter values thought to be impacted by drug

Mechanisms

Explanation for increase in extracellular dopamine and DOPAC levels

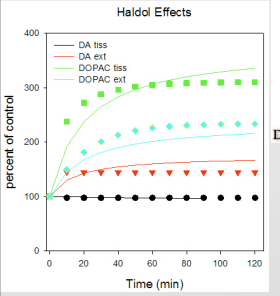
- –↑ DAext by ↑ Exocytosis – requires 1.7 fold increase in cytosolic synthesis to maintain steady state
- –↑ DOPACext by ↑DOPAC secretory synthesis by 200%
- –Produces about 150% increase in tissue DOPAC
- –Produces about 180% increase in total dopamine synthesis
- –Mechanism completely explains the effects of sulpiride using processes known to be regulated by D2 receptors

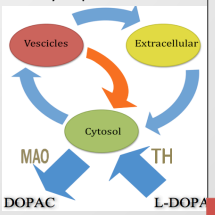




Explanation of variable tissue DOPAC and dopamine synthesis

- –↑ leak + ↑ cytosolic dopamine synthesis = ↑ cytosolic DOPAC
- –For haloperidol, produces 300% increase in tissue DOPAC and 380% increase in total dopamine synthesis
- –Non-D2 antagonist effects – second recycle process

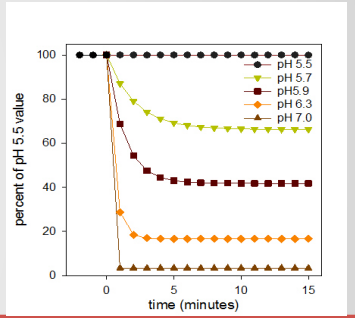




Leak Support

Effects of vesicle alkalinization

- •Literature data support antipsychotic effects on vesicles
  - –Haloperidol (and some other antipsychotics) alkalinize vesicles
    - ○ Moriyama, Y. *Arch Biochem Biophys* 305:278-281, 1993.
    - ○ Rayport, S. *J Neurochem* 65:691-703, 1995.
- •Our laboratory has previously modeled the increase of pH in vesicles showing an increased efflux of dopamine as the figure below shows



Conclusion

- •D2 modulates exocytotic rate
- •D2 modulates dopamine synthesis in DOPAC secretory synthesis complex for DOPACext
- •Cytosolic dopamine synthesis is modulated by level of dopamine in vesicles.
  - –↑ Leak = ↑ in cytosolic dopamine synthesis
- •Weak, lipophilic base controls DOPAC tissue and total synthesis
- •New synthesis regulatory mechanism = dopamine in vesicle is monitored and synthesis adjusts to keep constant level
- •Tissue DOPAC is not an accurate indicator of dopamine utilization (signaling)

DRUG	DA_syncyt	DA_synsec	DA_syntot	Leak value	DOPACtis
Control	2.88	1.35	4.23	2.7E-04	18,000
Sulpiride	4.34	2.84	7.16	2.7E-04	26,500
Clozapine	6.5	2.02	8.52	3.9E-04	42,700
Haloperidol	12	3.17	15.17	5.4E-04	80,000

This table shows stimulation values of three antipsychotic drugs